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MARKED-UP VERSION OF SPECIFICATION

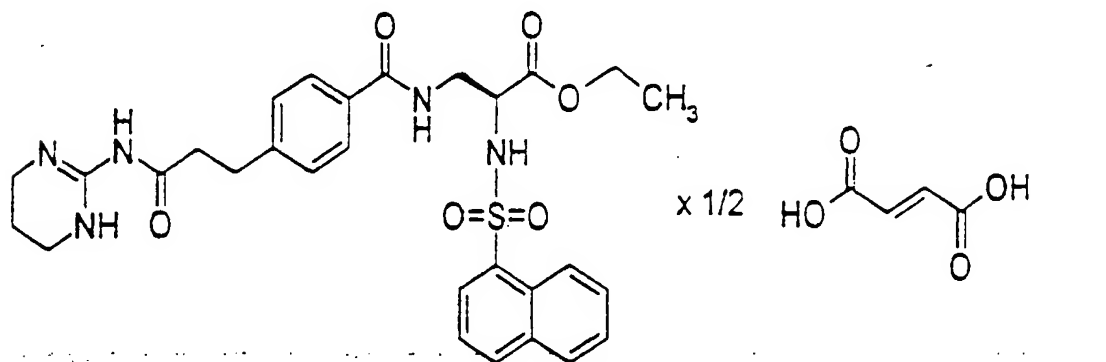
1,4,5,6 -TETRAHYDOPYRIMIDINE DERIVATIVE AS A VITRONECTIN INHIBITOR

—This application is a 371 of PCT/EP00/06504 filed July 8, 2000.—

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The present invention relates to ethyl (2S)-2-(naphthalene-1-sulfonylamino)-3-(4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoylamino)propionate hemifumarate of the formula I,

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and to a process for its preparation comprising reacting 4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoic acid or a derivative thereof and ethyl (2S)-3-amino-2-(naphthalene-1-sulfonylamino)propionate. The compound of the formula I is a valuable pharmaceutical which can be used, for example, in the treatment or prophylaxis of diseases which can be influenced by inhibiting the vitronectin receptor, in particular of bone diseases such as osteoporosis. The invention furthermore relates to chemical intermediates useful for the preparation of the compound of formula I.

Bones are subject to an ongoing dynamic renovation process comprising bone resorption and bone formation. In certain bone diseases like osteoporosis bone resorption predominates over bone formation thus leading to lower bone mass and enhanced fragility. Bone resorption and bone formation are controlled by types of cell specialized for these purposes. Bone resorption is based on the destruction of bone

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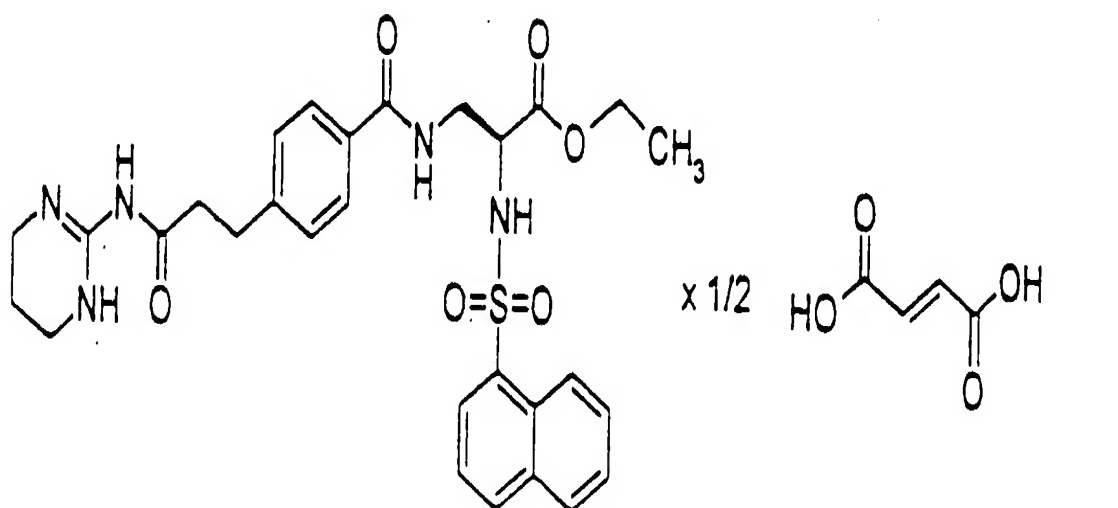
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MARKED-UP VERSION OF CLAIMS

Patent claims

1. Ethyl (2S)-2-(naphthalene-1-sulfonylamino)-3-(4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoylamino)propionate hemifumarate of the formula I

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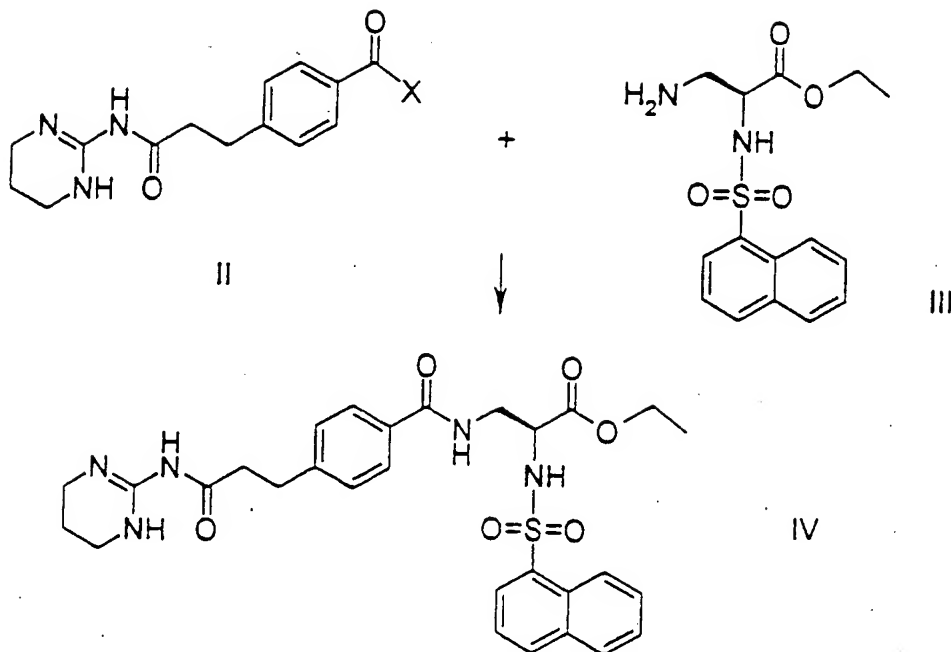
2. A pharmaceutical composition ^{for treating bone disease} comprising ^{low amount of} the compound of the formula ~~as~~ ~~claimed in claim 1~~ and a pharmaceutically acceptable carrier.

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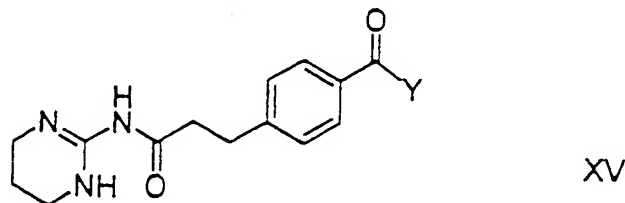
^{sufficient to treat bone disease}

3. A process for the preparation of ethyl (2S)-2-(naphthalene-1-sulfonylamino)-3-(4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoylamino)propionate ~~of the formula IV~~ or a salt thereof, comprising reacting 4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoic acid or a derivative thereof of the formula ~~II~~ wherein X is hydroxy or a leaving group, ^{with} and ethyl (2S)-3-amino-2-(naphthalene-1-sulfonylamino)propionate of the formula ~~III~~, or a salt or salts of any one or both of

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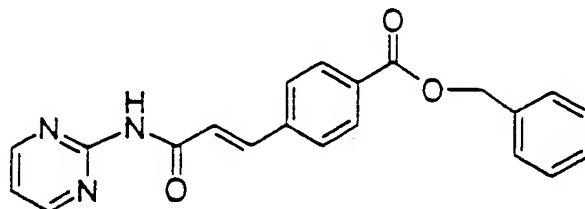
4. The process ~~as claimed in claim 3~~ ^{of} ~~characterized in that X is~~ ^{wherein} ~~chlorine~~ ²¹.
5. The process ~~as claimed in claims 3 and/or 4~~ ^{of} ~~characterized in that subsequently to~~ ^{product} ~~the reaction of the compounds of the formulae II and III an acid is employed and an~~ ^{reacted with an acid to form} ~~the acid addition salt of the compound of formula IV with said acid is prepared.~~
6. The process ~~as claimed in one or more of claims 3 to 5~~ ^{characterized in that ethyl}
- 10 (2S)-2-(naphthalene-1-sulfonylamino)-3-(4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbonyl)ethyl)benzoylamino)propionate hemifumarate is prepared.
7. A compound of the formula ~~XV~~,



wherein Y is hydroxy^{or} chlorine or bromine, or a salt thereof.

8. A compound of the formula ~~XV as claimed in claim 7~~ which is 4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoic acid or 4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoyl chloride or a salt ^{thereof} ~~of any of these compounds~~.

9. Benzyl 4-(2-(pyrimidin-2-ylcarbamoyl)vinyl)benzoate of the formula ~~XIII~~ or a salt thereof.



XIII

or a salt thereof

10. A process for the preparation of 4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoic acid or a salt thereof, comprising hydrogenating benzyl 4-(2-(pyrimidin-2-ylcarbamoyl)vinyl)benzoate or a salt thereof.

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